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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,697	10/05/2006	Jurgen Wagner	33714-US-PCT	2925

1095 7590 07/06/2010

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 101/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
07/06/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,697	WAGNER ET AL.	
	Examiner	Art Unit	
	WALTER E. WEBB	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5 and 15-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 15-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/1/2009 has been entered.

Applicants' arguments, filed 12/1/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

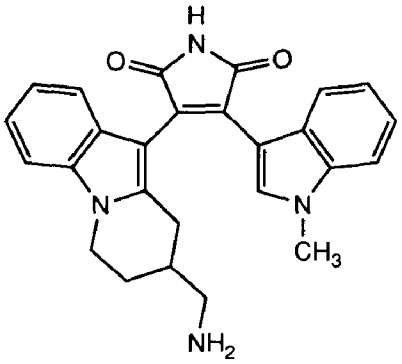
New

1) Claims 5, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heath et al. (US 5,545,636) in view of Bradshaw et al., (Agents Actions 1993).

Heath et al. teaches protein kinase C inhibitors and their use in treatment of conditions in which protein kinase C has demonstrated a role in the pathology. Conditions recognized by Heath et al. include: diabetes mellitus, ischemia, inflammation, central nervous system disorders, cardiovascular disease, dermatological disease, Alzheimer's disease and cancer (see col. 11, lines 60-67). The compound 3-(1-methyl-1H-indol-3-yl)-4-[1-(piperidin-4-yl)-1H-indol-3-yl]-pyrrole-2,5-dione is taught at col. 53, Example 68, lines 19-32, as being one of those inhibitors. Applicant as admitted in the specification that the instant compounds may be synthesized as described in Heath et al. (see specification at pg. 8, 3rd paragraph). The compounds of Heath et al. are identified as bis-indolemalemides (see col. 2, line 25, and col. 10, lines 11-16).

Heath et al. does not teach treatment of transplant rejection.

Bradshaw et al. cures the deficiencies of Heath et al. insofar as it teaches the therapeutic potential of protein kinase inhibitors, specifically bis-indolylmaleimides showing a high degree of selectivity for PKC. Bradshaw identifies Ro 31-8425 and Ro-31-8830 as examples, which read on the compound formula of Heath et al. Ro 31-8425



has the following structure: Ro 31-8425 (see Figure 2 at pg. 142). Bradshaw teaches that this class of compound inhibit T-cell proliferation (see section on Rheumatoid arthritis at pp. 136-137) and because of this function, they would be useful for treating transplant rejection (see pg. 138, left column, 2nd paragraph). Bradshaw also teaches the use of these compounds in treating the diseases listed in Albert et al. as well. In regard to transplant rejection Bradshaw also teaches that this disease has been successfully treated with other immunosuppressive agents such as cyclosporine A (**claims 15, 16**) (see Id.).

It would have been obvious to a person having ordinary skill in the art at the time of applicant's invention to have used the PKC inhibitor bis-indolemaleimide compounds of Heath et al. in a method for treating transplant rejection, since PKC inhibitor bis-indolemaleimides, as a class, have been recognized as useful in treating transplant rejection, as taught by Bradshaw et al. The artisan would also have a reasonable

expectation of success in treating transplant rejection, since transplant rejection is a type of inflammation, and Heath et al. teaches that the compounds are useful for treating inflammation.

Generally, it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose; the idea of combining them flows logically from their having been individually taught in prior art. See MPEP 2144.06. Thus, combining the compounds of Heath et al. with cyclosporine A as claimed in the instant invention would have been prima facie obvious since they are both taught to be useful for treating transplant rejection.

2) Claims 5, 15, 16 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heath et al. (US 5,545,636) in view of Albert et al., (US 2004/0053949).

Heath et al., taught above, differs from claims 5, 15, 16 and 20-22 insofar as it does not teach a method of treating tissue transplant rejection or prolonging graft survival (claim 20).

Albert et al. also teaches PKC inhibitor bis-indolemaleimide compounds, overlapping in scope with the compounds of Heath et al., and provides further teaching on the uses of these compounds in regard to their ability to inhibit PKC, such as treating T-cell mediated acute or chronic inflammatory diseases, auto-immune diseases, and graft rejection (transplant rejection) (see Abstract). Albert describes a transplantation

where graft survival significantly increased when administered a compound of Albert et al. at a dose of 30 mg/kg/day (see paragraph [0244]). Albert also teaches combining the compounds with cyclosporine A, rapamycin, (**claims 21, 22**) or other immunosuppressants for treating allo- or xenograft acute or chronic rejection, or inflammatory disorders (see paragraph [0255]).

It would have been obvious to a person having ordinary skill in the art at the time of applicant's invention to have used the PKC inhibitor bis-indolemaleimide compounds of Heath et al. in a method for prolonging graft survival and/or treating transplant rejection, since PKC inhibitor bis-indolemaleimides, have been recognized in the prior art for doing so, as taught by Albert et al. The artisan would reasonably expect the compounds having similar structure and function to be useful for the same purposes, i.e. prolonging graft survival and/or treating transplant rejection. It would have also been obvious to combine the compounds of Heath et al. with cyclosporine A, since Albert teaches combining bis-indolemaleimide compounds with cyclosporine A, for treating diseases and conditions described therein.

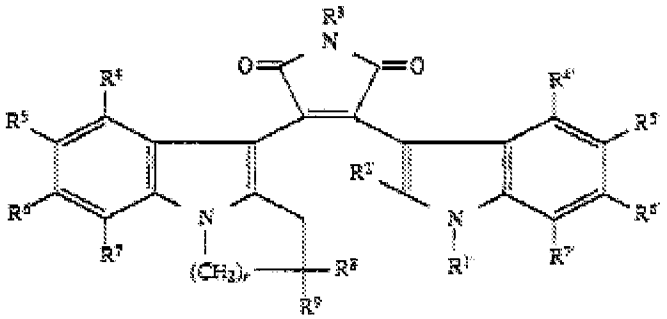
Previous

2) Claims 17-19 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Heath et al. (US 5,545,636) and Albert et al., (US 2004/0053949) in view of Goekjian et al., (Expert Opinion Investigative Drugs 2001).

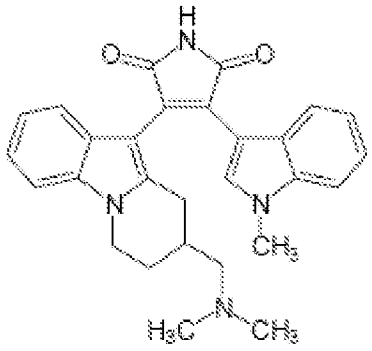
Applicant argues that in order to establish a prima facie case of obviousness, the office must establish that the compounds of Heath et al. are equivalent to the

compounds of Albert. However, the compounds of Heath et al. and Albert are equivalent, since they share the same basic structure and are taught to be useful for treating inflammation.

Applicant argues that Ro 32-0432 is structurally quite different from the claimed compounds. However, the compounds of Albert et al. share the basic structure below,



, which strongly resembles the structure of Ro 32-0432[1],



. Given the very close structural and functional similarities of the compounds of Heath et al. and Ro 32-0432, i.e. inhibition of PKC having same isozyme selectivity, the artisan would reasonably expect the compounds of Heath et al. to be useful in a method for treating graft-versus-host-disease as well.

Applicant argues that Goekjan does not motivate the artisan to arrive at the instant invention since, Goekjan teaches that Ro 32-0432 was abandoned during

development in favor of more selective inhibitors. However, Goekjan was merely speculating on the development of Ro 32-0432. The reference states, "Although Ro 32-0432 is orally active and well tolerated, these agents ***may*** have been abandoned in favour of more selective inhibitors already available in clinical trials" [emphasis added] (see pg. 2131, right column, second paragraph). Clearly Goekjan et al. does not make a definitive statement in regard to the status of Ro 32-0432.

Heath et al. teaches that its compounds are isozyme selective inhibitors of beta-1 and beta-2 isozymes of PKC, and as previously indicated, graft-versus-host disease (GVHD) is recognized in the prior art as a PKC-linked immunodisorder.[2] Heath et al. does not teach a method of treating graft-versus-host disease. However, this deficiency is cured by Goekjian et al., insofar as it teaches the use of a compound having selective inhibition for beta-1 and beta-2 isozymes of PKC, Ro 32-0432, for treating graft-versus-host response models in rats (see Goekjian et al. at pg. 2131, left column, 2nd paragraph; see also Table 4, at pg. 2128 for relation to isozymses of PKC). Ro 32-0432 is also a bis-indolemaleimide compound. It would have been obvious to a person having ordinary skill in the art to use the compounds of Heath et al. in a method for treating graft-versus-host disease, since Goekjian et al. teaches using a bis-indolemaleimide compound to treat graft-versus-host disease.

Applicant continues to argue about isozyme sensitivity, when this feature is not instantly claimed. Clearly the same class of compound is being discussed by each of the cited references, and they all overlap in scope in regard to function, i.e. PKC

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[1] See CALBIOCHEM product information for Ro-32-0432, Dec. 1999.

inhibition and inflammation. The art provides further information about the type of diseased treated under the umbrella of inflammation, namely graft-versus-host disease and transplant rejection. Despite the isozyme selectivity, the compounds would continue to be useful for treating inflammation. Goekjian et al. provides further support of this insofar as it teaches the use of a PKC inhibitor, having selective inhibition for beta-1 and beta-2 isozymes of PKC, for treating graft-versus-host disease.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 8:00am-4:00pm Mon-Fri EST.

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[2] Hong Hu, "Recent discovery and development of selective protein kinase C inhibitors." Drug Discovery Today 1996:1(10); at pg 445, right column, 1st paragraph.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Walter E. Webb
/Walter E Webb/
Examiner, Art Unit 1612

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612